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In This Issue

Use of Complementary and Alternative Medicines by HIV-Infected Patients

Introduction

HIV-related complementary therapies have been defined as the "scientific and nonscientific interventions that diverge from the accepted traditional treatment of HIV infection."[1] Other terms for this field include herbal remedies; alternative therapies; unorthodox, unconventional, and holistic medicine; and naturopathy. Complementary therapy may take the form of meditation, massage, acupuncture, spiritual healing, and other nonpharmacologic therapies, but is usually associated with dietary supplements, vitamins, and herbs. The usage of complementary and alternative medicines among the general public has dramatically increased in the past several years. Recent estimates indicate that nearly half of Americans used such products in 1997 at a cost of over $27 billion.[2] This widespread use is also apparent in the HIV-infected population. A telephone survey of 180 HIV-infected patients reported that 68 percent used complementary medicines.[3] In addition, patients visited their complementary medicine provider an average of 12 times per year, nearly double the number of visits to their traditional healthcare provider (7 visits). Other studies evaluating use of complementary medicines demonstrated that between 27 percent and 100 percent of HIV-infected patients use these products, with an average of approximately 35 percent.[4] While the specific therapies vary widely, studies indicate that African-Americans and Hispanics are less likely to use complementary medicines than whites, and lack of a university education is also associated with lesser use. Of interest, the percentage of patients using complementary medicines has not changed appreciably with the expanded availability of antiretroviral drug options. One survey performed when only zidovudine was available showed an average usage of 40 percent of patients,[5] which is comparable to a more recent survey demonstrating that 39 percent of HIV-infected patients used complementary therapies.[6]

Patients' Expectations

The reasons for this extensive use vary among HIV-infected patients (Table 1). Expectations for these therapies appear to be high. In one survey, approximately half of patients expected these therapies to slow the progression of disease or to provide "better immunity." Approximately one third of patients believed the complementary therapies would be synergistic with antiretrovirals or reduce HIV-related symptoms. Twenty-one percent of patients expected complementary medicine to provide a cure.[5]

Concerns

Table 2 shows the most commonly used dietary supplements and herbs and their purported uses. Herbal products are considered "dietary supplements" or "food products" by the U.S. Food and Drug Administration and are not subject to the same stringent regulations imposed on other over-the-counter and prescription medications. As a result, there is a general lack of information regarding the pharmacology, pharmacokinetics, drug interactions, efficacy, and safety of these products. Even more alarming is the lack of quality control in the manufacturing of these products. An evaluation of 24 ginseng products demonstrated that 33 percent contained no active ingredient while the others had large variations in the amount.[7] Similarly, a study of 44 feverfew products demonstrated

no active component in 22 percent.[8] Thomas Moore, writing in *The Washingtonian,* appropriately stated, "Never have so many people consumed so many medical products about which we know so little."

A number of alternative products have been reported to either have antiviral activity or immune-stimulating effects. Dextran sulfate, SPV-30, high-dose vitamin C, compound Q, and curcumin have claims of activity and, in some cases, data suggesting some activity are available.[1] However, these studies are the exception rather than the rule. Overall, there is limited literature support for the use of any of these products to treat HIV infection.

What is clear is that certain products have been shown to be harmful. Table 3 lists those products associated with severe adverse effects. There has been a general misconception among the public that because a product is "natural," it therefore is also safe and free from side effects and drug interactions. This widely held view is unfortunately untrue. Many of these adverse effects may overlap with antiretroviral toxicities, complicating the identification and management of side effects. Recent data are also available demonstrating important interactions between complementary medicines and antiretrovirals. St. John's wort, a popular treatment for mild to moderate depression, was shown to decrease indinavir concentrations by over 50 percent in healthy volunteers.[9] This may occur because of induction of CYP3A4 or through alteration of p-glycoprotein. A recent case report also showed that St. John's wort decreased nevirapine concentrations by approximately 20 percent.[10] These types of interactions could lead to suboptimal blood concentrations of the antiretroviral agent and the subsequent development of resistance and treatment failure.

Other dietary supplements have also been shown to affect CYP450 in animal studies. Garlic, ginseng, and milk thistle have all been shown to alter drug metabolism, although there are currently limited data in humans. A preclinical study in rats demonstrated that single doses of garlic oil (500 mg/kg intraperitoneally [i.p.]) resulted in a significant depression of hepatic CYP450, aminopyrine N-demethylase, and aniline hydroxylase activity.[11] Of interest, multiple dosing (50 mg/kg i.p.) for 5 days led to a significant increase in hepatic cytochrome P450. This study demonstrates the complexity of studying drug interactions with complementary medicines: inadequate exposure to the herbal/alternative drug may lead to the demonstration of either no effect or the opposite effect to that seen with general use in patients. From a clinical standpoint, a recent abstract described case reports of 2 HIV-infected patients who developed severe gastrointestinal toxicity from ritonavir after ingesting garlic supplements.[12] Animal studies have suggested some effect of milk thistle on the cytochrome P450 system.[13-15] However, a clinical study examining the effect of 28 days of therapy with silymarin showed no effect on the metabolism of aminopyrine and phenylbutazone.[15] It should be noted that the dose of silymarin used in this trial was lower than that commonly used in clinical studies and for treatment of liver disease. Ginseng also appears to have some effect on metabolism via the CYP450 system in animal models.[16,17]

Table 1. Common Reasons for Use of Complementary Therapies

- Sense of desperation
- Sense of empowerment
- Distrust of medical establishment
- Frustration with the pace of research, drug approvals
- Eligibility limitations of clinical trials
- Easy access to Buyers Clubs and Treatment Networks
- Toxicities of conventional drugs
- Perception that therapies are nontoxic
- Claims in lay press of effectiveness

Table 2. Commonly Used Dietary Supplements and Herbs

Product	Use
Echinacea	Common cold, influenza
Garlic	Beneficial cardiovascular effects
Ginkgo biloba	Improved circulation
Kava	Anxiety
Milk thistle	Hepato-protective effects
SAMe	Depression
Saw palmetto	Benign prostatic hypertrophy
St. John's wort	Depression
Valerian	Mild sedative

Addressing Patients' Use of Complementary Products in Your Practice

It is unrealistic to ask patients not to use complementary products, since many will continue to do so without informing their provider. Many patients believe that these products do indeed provide benefit and are important as adjunctive therapies to their HAART regimen. The following are some suggestions regarding patient-physician communication with complementary therapies:

1. **Perform a complete drug history.** Ask patients specifically about their use of complementary therapies, including herbs, acupuncture, massage therapy, OTC agents, and dietary supplements.
2. **Collect and record data concerning complementary medicine use.** Healthcare providers should note the dates at which the patients initiated and discontinued these products. These dates can then be compared with the onset or resolution of adverse effects and any change in the immunologic response or virologic response to therapy.
3. **Listen to your patients and support them in a nonjudgmental fashion.** It is important to provide advice and steer patients away from unsafe therapies or those obtained from unreliable sources.
4. **Keep abreast of the latest information.** The healthcare provider should be a resource to the patient. The clinic, hospital, or physician's office should be a place where the patient can receive accurate, unbiased information. One study demonstrated that employees of health

food stores freely gave advice on treatment with herbs to HIV-infected patients but did not discuss adverse effects, despite the fact that many of the recommended products had known toxicities.[20]

Where to Find Additional Information

Numerous Web sites provide information on herbal remedies.[21] Some of these sites require a subscription while others are free. However, as often is the case, "you get what you pay for." Sites that charge, such as http://www.naturaldatabase.com, are frequently updated and provide references. It may well be worth paying a modest fee to receive reliable data. A number of peer-reviewed medical journals, such as the Journal of Complementary and Alternative Medicine, are also available and indexed on Medline.

Conclusions

An interesting paradox has been established. There is a great need for research in this area, but the multiple legal, political, and scientific issues complicate the design and funding of such projects. If an investigator wants to evaluate an herb in HIV-infected patients, how does one decide which specific brand to choose? In addition, there may be dozens or even hundreds of individual constituents in a specific herbal product. It is clearly not feasible to identify which component is responsible for the drug's beneficial or negative effects. Research into this area is unlikely to be funded by the pharmaceutical industry: A request to a drug company to fund a study of the interaction between milk thistle and their specific antiretroviral is likely to be received by amused rejection. Similarly, the likelihood that the billion dollar per year herbal industry would fund this research is remote, since negative findings could harm their record sales. It will be necessary to use public funds to address the issues of safety and efficacy with complementary medicines in the HIV-infected population. Several laboratories, including the National Institutes of Health, are beginning to address the magnitude of this issue.

Complementary therapies will continue to be widely used in HIV-infected patients since FDA-approved antiretrovirals remain problematic with regard to resistance, toxicity, food restrictions, and formulations. Clinicians need to ask about herbal remedies and include these products in the evaluation of adverse effects and response to therapy. Efforts to better understand the pharmacology of complementary medicines are clearly needed.

Table 3. Complementary Medicines With Harmful Effects[18,19]

Product	Toxicity
Borage	Potential for hepatotoxicity due to toxic alkaloids
Calamus	May contain beta-isoasarone, associated with nephrotoxicity and convulsions
Chaparral	Acute hepatitis, kidney, and liver failure
Coltsfoot	Hepatotoxicity, phototoxicity
Comfrey	Veno-occlusive disease
Ephedra	Increased blood pressure, arrhythmias, psychosis, heart failure
Germander	Hepatitis, liver cell necrosis
Life Root	Veno-occlusive disease
Sassafras	Hallucinations, vomiting, tachycardia, stupor, paralysis

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Did You Know ...

- That you can access the latest safety information from the Food and Drug Administration website? To access "Dear Health Professional" letters, other safety notifications, and labeling changes related to drug safety, just point your browser to *www.fda.gov* and click on "MedWatch." MedWatch is the FDA's medical products reporting program.
- That you can receive immediate e-mail notification of new material as soon as it is posted on the MedWatch website? Just send a subscription message to fdalists@archie.fda.gov. In the message body enter: *subscribe medwatch* and your e-mail address.

Formulary Update

The Pharmacy and Therapeutics Committee recently approved the following formulary changes:

Additions

- Dexrazoxane (Zinecard), an injectable cytoprotective agent
- Mirtazepine (Remeron), an oral tetracyclic antidepressant
- Rapacuronium (Rapalon), an injectable nondepolarizing neuromuscular blocker
- Diphtheria and tetanus toxoids and acellular pertussis vaccine (Infanrix), an injetable vaccine
- Poliovirus vaccine, inactivated (IPV), an injectable vaccine
- Valproate sodium (Depacon), an injectable anticonvulsant
- Metoprolol (Toprol XL), an oral (extended-release) beta-adrenergic blocker
- Pneumococcal 7-valent conjugate vaccine (Prevnar®), an injectable vaccine
- Linezolid (Zyvox), an oral and injectable oxazolidinone antibiotic (Use of this agent requires Infectious Diseases Consult Service approval.)

Deletions

- Poliovirus vaccine, live (OPV), an oral vaccine

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